References

1. Darwazah A, Kiswani M, Ismail H, Hawari M, Awad S. Aorto-right atrial fistula: a complication of prosthetic aortic valve endocarditis. A case report. J Heart Valve Dis 2006; 15: 142-5.
2. Shah BN, Livesey SA, Rakhit DJ. Aorto–atrial fistula in the absence of infective endocarditis diagnosis by 2- and 3-Dimensional transesophageal echocardiography. Tex Heart Inst J 2012; 39: 146-7.
3. Chandra S, Vijay S, Kaur D, Dwivedi S. Congenital aorta right atrial fistula: successful transcatheter closure with the Amplatzer occluder. Pediatr Cardiol 2011; 32: 1057-9.
4. Ece I, Üner A, Cüce F, Şahin M. Transcatheter closure of tortuous aorto-right atrial fistula. Cardiovasc Interv Ther 2015;30:151-4.
5. Elwatidy AF, Galal AN, Rhydderch D, Ashmeg AK. Aorto-right atrial fistula. Ann Thorac Surg 2003; 76: 929-31.
6. Ho AB, Magee AG, Hayes N. Descending thoracic aorta to right atrial fistula: Presenting with neonatal collapse. Catheter Cardiovasc Interv 2017 May 30. Epub ahead of print.
7. Gajjar T, Voleti C, Matta R, Iyer R, Dash PK, Desai N. Aorta-right atrial tunnel: clinical presentation, diagnostic criteria, and surgical options. J Thorac Cardiovasc Surg 2005; 130: 1287-92.
8. Arnett EN, Roberts WC. Valve ring abscess in active infective endocarditis; frequency, location and clues to clinical diagnosis from study of 95 necropsy patients. Circulation 1976; 54: 140-5.
9. Sakakibara S, Konno S. Congenital aneurysms of sinus of Valsalva. A clinical study. Am Heart J 1962; 63: 708-19.

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A novel mutation in the desmoplakin gene in two female siblings with a rare form of dilated cardiomyopathy: Carvajal syndrome

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Introduction

Carvajal syndrome is a cardiocutaneous syndrome characterized by dilated cardiomyopathy (DCM), woolly hair, and keratoderma (1). Here we present the case of two female siblings with Carvajal syndrome and a new homozygous frameshift mutation in desmoplakin (DSP).

Case Report

A 5-year-old female patient, who was the first child of second-degree consanguineous parents, with no significant medical history was admitted with complaints of malaise and abdominal pain that persisted for 3 months. She had tachypnea and tachycardia. Her vital signs were as follows: heart rate, 140 beats/min; respiratory rate, 32 breaths/min; and blood pressure, 95/64. Gallop rhythm and jugular venous distension were noted. The liver and spleen were palpable 10 and 5 cm below the costal margin, respectively, and edema was present on the legs. Laboratory findings were as follows: brain natriuretic peptide, 2667 pg/mL (normal <100); creatine kinase-MB, 8.1 ng/mL (normal <6.3); and cardiac troponin I, 0.03 ng/mL (normal <0.06); complete blood count and other biochemical laboratory findings were normal except for mildly elevated liver enzyme levels. Echocardiography revealed markedly dilated cardiac chambers, prominently the left chambers, marked left ventricular dysfunction (ejection fraction: 25.7%, fractional shortening: 13%, LVIDd: 47 mm) and moderate mitral regurgitation. After being treated for congestive heart failure (CHF) for 2 years, left ventricular assist device was implanted, and on the 501th day after implantation, the patient underwent heart transplantation. The biopsy of the heart revealed widespread multifocal myofibrillar damage and interstitial fibrosis. The patient's 18-month-old younger sibling, who was successfully treated for neuroblastoma at the age of 1 year, was treated for DCM for 1 year and was referred to our hospital at the age of 6 years. Besides signs of CHF, peculiar woolly hair (Fig. 1a), palmoplantar (1b & 1c) keratoderma, and wart-like lesions on the hand were strikingly forefront in both siblings. Both patients had normal eyelash, eyebrow, and nail and teeth development. At admission, both siblings had ventricular arrhythmias, voltage suppression, and left-sided cardiomyopathy. All screening test results for DCM (metabolic screening tests, viral serologic tests, and upper respiratory viral and bacterial panel) were normal. Genetic screening revealed a normal JUP gene and a new homozygous frameshift mutation, c.4650_4651delTG (p. V155Efs*75), in DSP in both siblings. Both parents were also heterozygous for the DSP frameshift mutation. The parents did not have any abnormal echocardiographic, electrocardiographic, or cutaneous findings . The younger sibling has been on anticongestive medication for 4 years and the older sibling had a successful heart transplantation 23 months ago.

Discussion

DCM can be caused by a variety of factors or may be inherited as a hereditary disease. Although most commonly cytoskeletal, sarcomere, or Z-disk proteins are affected, mutations in ion channels and desmosome-encoding genes have also been reported (2).

Desmosomes are major cell adhesion junctions that provide mechanical stability, and desmoplakin is the most abundant constituent (3). Dysfunction of desmosomes leads to cell death and

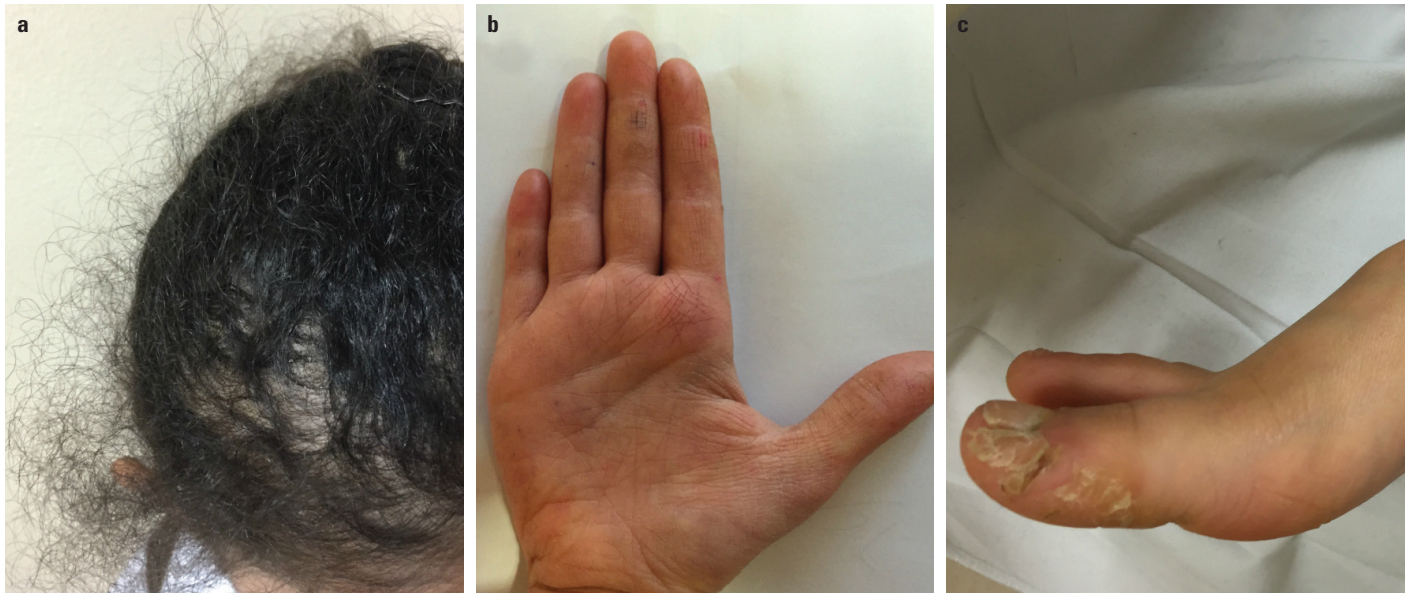

Figure 1. Cutaneous findings of Carvajal disease in our patient.
(a) Peculiar woolly hair, (b) palmar keratoderma, and (c) plantar keratoderma

eventually to fibrosis (4). Mutations in genes encoding desmosomal proteins have been associated with DCM and arrhythmogenic right ventricular disease (ARVD) (2).

Dilated cardiomyopathy with woolly hair and keratoderma (DCWHK), also known as Carvajal disease, is an autosomal recessive cardio-cutaneous syndrome caused by mutations in DSP, which encodes desmoplakin on chromosome 6p24 (1). Naxos disease, in which palmoplantar keratoderma, woolly hair, and ARVD are observed, is due to a mutation in JUP (2). Molecular mechanisms underlying these diseases are heterogeneous and poorly understood. Genetic screening is crucial for differential diagnosis because of significant overlapping.

DCWHK was first reported by Carvajal by examining 18 patients. All patients were born with woolly hair, and keratoderma appeared at 10 months of age or later. The first cardiac abnormalities were electrocardiographic abnormalities in asymptomatic patients who later displayed echocardiographic and hemodynamic features of DCM (1).

Norgett et al. (5) described the first recessive human DSP gene mutation 7901delG. Further, homozygosity for a 1-bp deletion (2) and, recently, a homozygous frameshift mutation, c.3924delG, and a homozygous missense mutation, c.7111C>A, in DSP gene have been reported (6).

Genetic screening of our patients revealed a novel homozygous frameshift mutation, c.4650_4651delTG (p. V155Efs*75), in DSP. The unaffected parents were also heterozygous for the DSP frameshift mutation.

Conclusion

Genetic screening is an important tool for the early diagnosis of disease in asymptomatic family members, along with cutaneous findings, which appear before the development of cardiomyopathy. Early diagnosis by genetic screening may be life-saving for these patients who are possible candidates for heart transplantation in future. Detection of new mutations and prenatal genetic counseling may help parents in their planning of a future family.

References

1. Carvajal-Huerta L. Epidermolytic palmoplantar keratoderma with woolly hair and dilated cardiomyopathy. J Am Acad Dermatol 1998; 39: 418-21. [CrossRef]
2. Rasmussen TB, Hansen J, Nissen PH, Palmfeldt J, Dalager S, Jensen UB, et al. Protein expression studies of desmoplakin mutations in cardiomyopathy patients reveal different molecular disease mechanisms. Clin Genet 2013; 84: 20-30. [CrossRef]
3. Green KJ, Parry DA, Steinert PM, Virata ML, Wagner RM, Angst BD, et al. Structure of the human desmoplakins. Implications for function in the desmosomal plaque. J Biol Chem 1990; 265: 2603-12.
4. Holthofer B, Windoffer R, Troyanovsky S, Leube RE. Structure and function of desmosomes. Int Rev Cytol 2007; 264: 65-163. [CrossRef]
5. Norgett EE, Hatsell SJ, Carvajal-Huerta L, Cabezas JC, Common J, Purkis PE, et al. Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. Hum Mol Genet 2000; 9: 2761-6. [CrossRef]
6. Molho-Pessach V, Sheffer S, Siam R, Tams S, Siam I, Awwad R. et al. Two Novel Homozygous Desmoplakin Mutations in Carvajal Syndrome. Pediatr Dermatol 2015; 32: 641-6.[CrossRef]

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